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Environmental and nutritional effects on the epigenetic regulation of genes

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Abstract

Major efforts have been directed towards the identification of genetic mutations, their use as biomarkers, and the understanding of their consequences on human health and well-being. There is an emerging interest, however, in the possibility that environmentally-induced changes at levels other than the genetic information could have long-lasting consequences as well. This review summarises our current knowledge of how the environment, nutrition, and ageing affect the way mammalian genes are organised and transcribed, without changes in the underlying DNA sequence. Admittedly, the link between environment and epigenetics remains largely to be explored. However, recent studies indicate that environmental factors and diet can perturb the way genes are controlled by DNA methylation and covalent histone modifications. Unexpectedly, and not unlike genetic mutations, aberrant epigenetic alterations and their phenotypic effects can sometimes be passed on to the next generation.

Keywords: Epigenetic; Environment; Toxicology; Nutrition; Genomic imprinting; DNA methylation; Biomarker

1. Genotype and epigenotype

The term 'epigenetic' is used to refer to stably maintained patterns of gene expression that occur without changes in the DNA sequence. Epigenetic regulation plays an important role in animal and plant development, and throughout adult life, and is required to achieve stable expression, or repression, of genes in specific cell types or at defined developmental stages. There are many covalent epigenetic modifications involved in keeping genes stably repressed, or active. Possibly the best studied epigenetic modification is DNA methylation. In the genomes of mammals, this covalent modification occurs at many of the cytosine residues that are followed by a guanine residue. In most cases, the acquisition and somatic maintenance of such 'CpG methylation' induces gene repression. However, there are also examples where DNA methylation at specific sequence elements permits the expression of neighbouring genes. Additionally, gene expression is determined by the organisation of the histones in the nucleosomes around which the DNA is wrapped. In recent years, many covalent modifications have been discovered to occur at the amino acids that constitute the N-terminal tails of histones. Alone, or in combination, these histone modifications are thought to be indispensable for the regulation of the continued repression, or expression, of genes. From extensive recent work, it follows that in particular histone acetylation and histone methylation are essential for the somatic maintenance of gene regulation [1,2].

When considering how different kinds of environmental stress can influence epigenetic mechanisms, it should be important to emphasize that the epigenetic modifications on DNA and chromatin constitute the link

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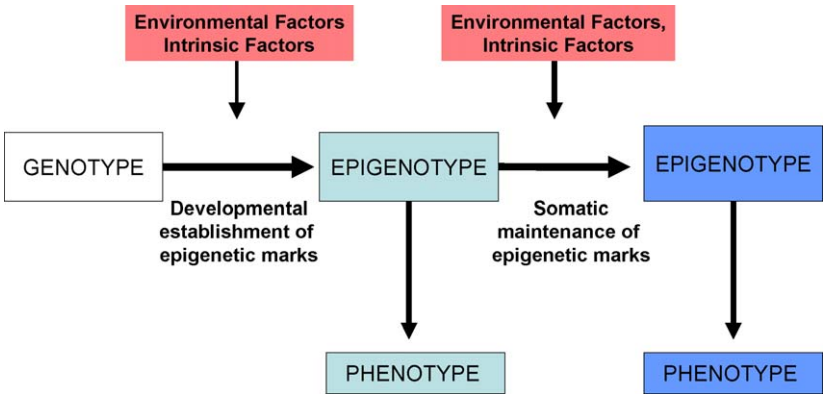

Fig. 1. The dynamic link between genotype, epigenotype, and phenotype. Heritable patterns of DNA methylation and other epigenetic modifications are established during development, in the different lineages of the embryo. This involves many different intrinsic mechanisms, and is influenced by the uterine environment as well. The resulting epigenotype(s) determines heritable gene expression, and thus the phenotype. Environmental, toxicological, and nutritional factors impact on the establishment and somatic maintenance of epigenetic patterns. This may alter the epigenotype, and can thus influences the phenotype.

between the genotype and the phenotype (Fig. 1). In specific cell lineages, and at defined developmental stages, chromatin at genes is modified in a way that leads to acquisition of constant gene repression, or activation. This developmental process is governed to a large extent by intrinsic factors, but it is now clear that environmental factors may affect epigenetic patterns as well [3]. The combination of the different epigenetic modifications at genes and non-coding sequences is commonly referred to as the epigenome, or the epigenotype. The epigenotype determines whether genes are maintained in a repressed state, or kept potentially active, and it influences the phenotype at birth. Importantly, epigenetic modifications need to be maintained throughout every cell cycle, in order not to alter the epigenotype(s). Intrinsic factors play important roles here, such as the methyltransferases that somatically maintain patterns of DNA methylation. However, environmental factors and nutrition could also have an impact on how faithfully patterns of epigenetic modifications are maintained throughout life. In case of aberrant environmental effects, or of stochastic shifts in intrinsic maintenance factors, the epigenotype may become altered. This may give rise to altered gene expression and, therefore, to an altered phenotype (Fig. 1). Thus, the phenotype is determined by the epigenotype, which may become altered during development, or in postnatal life, due to errors in intrinsic mechanisms, or due to environmental influences. So far, there are few studies addressing the environmental and toxicological effects on DNA methylation and histone modifications. Undoubtedly, this will be an important question for future research. The theme is elaborated in the current review, which focuses mostly on studies in the mouse, but gives human examples as well.

2. Genomic imprinting, an example of epigenetic regulation in mammals

In mammals, there are many examples of epigenetic repression or activation of genes [4]. These include: (a) X-chromosome inactivation, i.e. the inactivation of one of the two X chromosomes in female somatic cells [5]; (b) the allelic silencing occurring at imprinted genes, a group of key genes whose expression is dictated by whether they are inherited from the mother or the father; (c) the control of lineage-specific maintenance of gene expression at different loci; (d) the heritable repression of repeat elements of viral or retroviral origin [6].

Imprinted genes constitute a particularly attractive example of epigenetic regulation, since in the same cell, one of the two alleles is stably repressed by epigenetic modifications, whereas the other allele is maintained in an active state (Fig. 3). This allele-specific regulation is entirely determined by the parental origin of the allele, that is, by whether the gene is inherited from the mother or from the father. To date, some eighty genes have been found to be controlled by imprinting in humans and mice. Many of these play key roles in development, cellular proliferation and behaviour [7–9]. A characteristic feature of imprinted genes is that they are organised in clusters in the genome. These imprinting clusters are similar between humans and mice, and imprinting is evolutionarily conserved in other placental mammals as well [10–12]. Epigenetic deregulation of imprinted genes is